EXHIBIT 74

Document title:	(2) Adrian H on X: "As with the Bordey paper, this is actually a fantastic experiment $SAVA has done to determine just what kind of fantastical results a lab can come up with when given an inert compound targeting their pet protein" / X
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Adrian H @Adrian_H · May 5, 2023
So apparently this is the "evidential data for the biological activity of simufilam outside the field of neurogeneration" $SAVA teased about

endocrine-abstracts.org/ea/0090/ea0090...

amusingly, the senior author already has papers flagged on pubpeer @MicrobiomDigest

pubpeer.com/search?q=+Erik...

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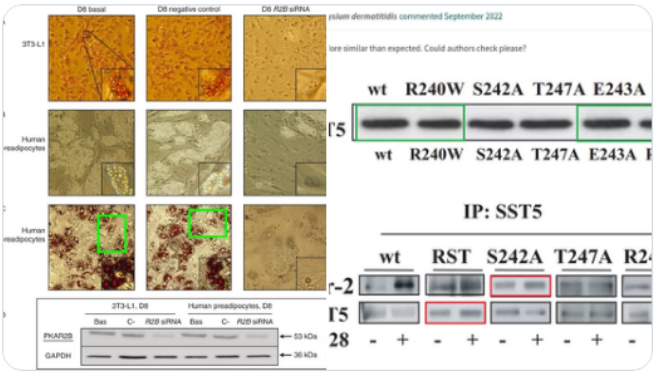
Adrian H @Adrian_H · May 5, 2023
Lindsay really knows how to pick'em



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Adrian H @Adrian_H · May 5, 2023
I also like how they talk about doing an assay to test drug combinations but they don't think it worth mentioning the concentration of any of the 'drugs' (let alone do a proper dose matrix to quantify synergy)

(Just my opinion as someone who once ran a lot of combo screens)


A novel filamin A-binding molecule may significantly enhance SST2 antitumoral actions in GH-secreting PitNET cells

Giusy Marra [1], Donatella Treppiedi [2], Genesio Di Muro [1,3], Federica Mangili [2], Rosa Catalano [1], Emanuela Esposito [1,4], Emma Nozza [1,4], Marco Locatelli [5,6], Andrea Lania [7,8], Elisa Sala [2], Emanuele Ferrante [2], Maura Arosio [1,2], Lindsay H. Burns [9], Giovanna Mantovani [1,2] & Erika Peverelli [1,2]

Author affiliations

The main target of pharmacological therapy for growth hormone (GH)-secreting pituitary tumors (GH-PitNET) is the somatostatin receptor type 2 (SST2). However, approximately half of patients treated with octreotide, an SST2 agonist, show a low response rate or are octreotide-resistant. Here we present mechanistic data that shows co-treatment with simufilam, a novel oral therapeutic candidate, enhances sensitivity to octreotide. We previously showed that the cytoskeleton protein filamin A (FLNA) is recruited to bind SST2 upon agonist stimulation, and this interaction is required for SST2 signaling in GH-PitNET cells. However, when phosphorylated at Ser2152, FLNA no longer enables SST2 signaling and all SST2 anti-tumor effects are abolished. Simufilam is a FLNA-binding small molecule shown to modulate FLNA's conformation and its interactions with partner proteins in disease states. We postulated that simufilam may restore FLNA's linkage to SST2 and therefore FLNA's ability to enable SST2 signal transduction. To test this hypothesis, we assessed simufilam's effects on FLNA phosphorylation, FLNA-SST2 complex formation, SST2 signal transduction, GH secretion and cell proliferation/apoptosis, in human primary cultured GH-PitNET cells and in the rat pituitary tumor cell line GH4C1. Simufilam treatment reduced FLNA phosphorylation on Ser2152 in GH4C1 cells (-28±13% after 10 min, $P<0.01$ vs basal) and in primary human GH-PitNET cells (-59%). Additionally, FLNA-SST2 complexes in GH4C1 cells fell below basal levels after 1h octreotide treatment (-29±6.8%, $P<0.05$ vs bas) but were still elevated after 1h co-incubation with octreotide+simufilam (135±19.7%, $P<0.05$ vs bas). Simufilam did not affect the ability of octreotide to inhibit GH secretion in GH4C1 or primary GH-PitNET cells that are *in vitro* responsive to octreotide; however, a combination of simufilam+octreotide reduced GH secretion in primary GH-PitNET cells that are *in vitro* resistant to octreotide ($n=2$) (-42±3.5%, $P<0.001$ vs bas). Simufilam slightly reduced cell proliferation (-15±10.1%, $P<0.05$ vs bas) and ERK phosphorylation (-21±18.8%, $P<0.05$ vs bas), while increasing cell apoptosis (+17.8±7.3%, $P<0.05$ vs bas) in the GH4C1 cell line. Interestingly, co-treatment with simufilam+octreotide in GH4C1 potentiated the pro-apoptotic effect of the single drugs (+13±5% octreotide, $P<0.001$ vs bas; +36.8±9.2% octreotide+simufilam, $P<0.01$ vs bas, $P<0.05$ vs octreotide or simufilam alone). In conclusion, simufilam reduced FLNA phosphorylation, enhanced and prolonged the octreotide-induced FLNA-SST2 interaction and promoted SST2 signal transduction in human primary cultured GH-PitNET cells. These data suggest that co-treatment with simufilam may enhance the efficacy of octreotide or other somatostatin analog drugs in the management of pituitary tumors.

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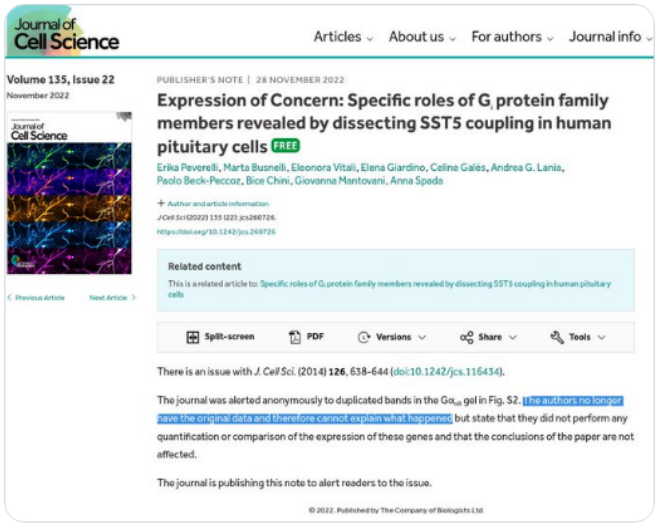

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Adrian H
@Adrian_H

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it takes a lot to impress me after Dr. Magna cum Laude's wikipedia antics (en.wikipedia.org/w/index.php?ti...) but $SAVA manages to always rise to new levels of delusional, incompetent bumbling

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